Triage in a Patch

FOLLOWING an explosion at a chemical plant, employees and neighbors may find themselves in a triage facility where a nurse will apply a small, disposable patch to each person's arm. In a few minutes, a simple color change in this colorimetric patch will indicate whether the person was exposed to dangerous levels of a toxic substance.

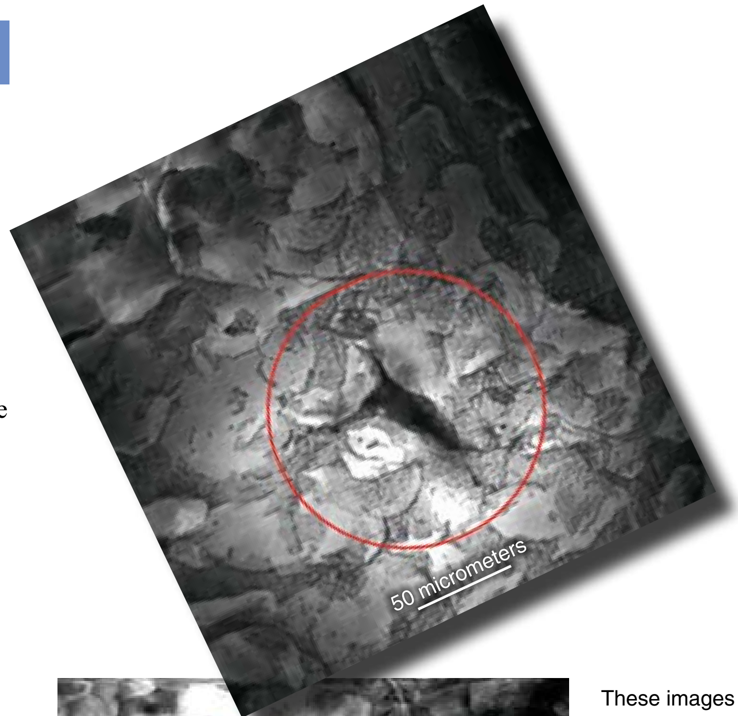
The patch contains hundreds of hollow silicon "microneedles," each of which draws fluid from the outer layer of skin by capillary action. The needles are so short—just a few hundred micrometers—that the patch is painless. Integrated into the Band-Aid®-size patch are various chemical processes for testing biological fluids. Research is under way at Livermore for this scenario to become a reality.

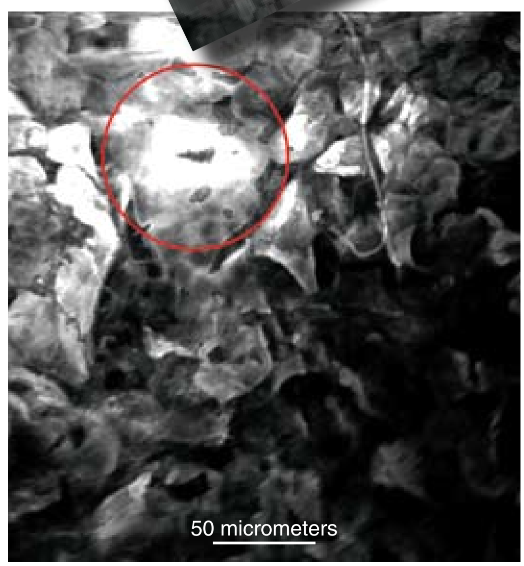
Painless Needles

Microneedles have been in development for nearly 20 years to replace painfully invasive hypodermic needles for delivering drugs. Today, a revolutionary needle geometry has been designed that allows for fluid flow both out of the skin and into it. While a graduate student at the University of California (UC) at Davis, Livermore biomedical engineer Erik Mukerjee led a team that expanded the potential uses for microneedles. Mukerjee was inspired while watching a nature television program about poisonous snakes. He noticed that most cobras inject their venom via a tiny channel behind each fang and thus was born the "snake fang" microneedle.

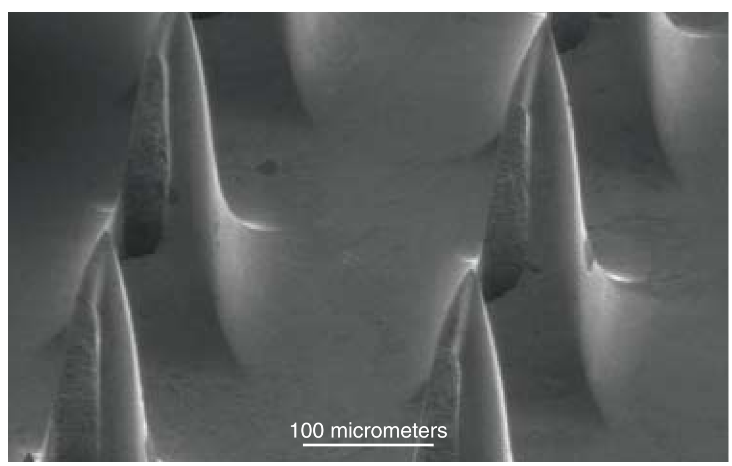
Using this novel microneedle design, the UC Davis team went on to develop a patch that could, for the first time, extract fluid from the body. If the fluid to be withdrawn is blood, the microneedles on the colorimetric patch need be only 350 micrometers long. If the target is interstitial fluid, which lies in the epidermis (the outer, nonvascular, nonsensitive layer of the skin), the microneedles can be even shorter—a mere 250 micrometers long. "We have an amazing amount of freedom during the microfabrication process," say Mukerjee, who now works in Livermore's Engineering Directorate. "We can easily modify the shape and length of the microneedles to suit a specific application."

Using a patch made of microneedles and tiny microchannels that lead to a common reservoir, the team tested the application by monitoring blood glucose in interstitial fluid. The needles on the patch were just long enough to enter the epidermis and collect a fluid sample. Says Mukerjee, "Although a 10-minute lag exists between glucose level changes in the blood and in the interstitial fluid, it is still the perfect fluid for glucose monitoring. The epidermis has only a few nerve endings and no blood capillaries. By targeting interstitial fluid, we can painlessly and continuously

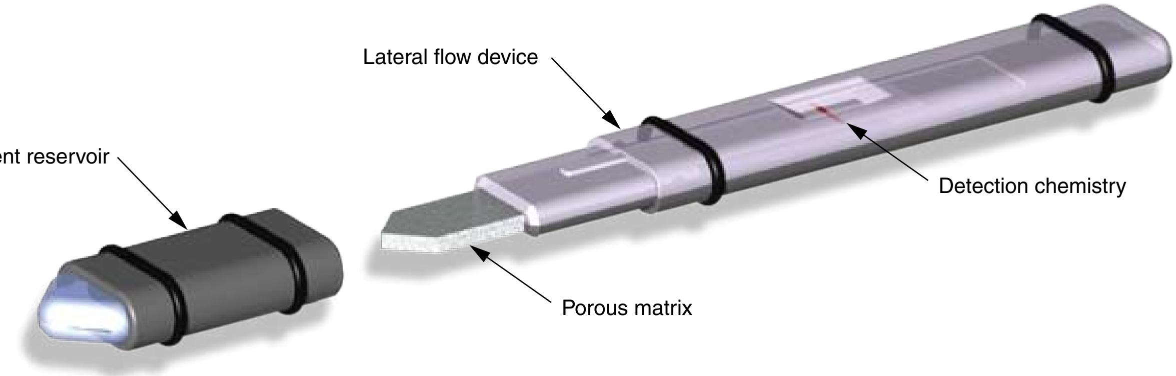




These images show the difference in the size of the hole made when human skin is pierced with a hypodermic needle (above) and with a microneedle (left). A microneedle makes a much smaller hole—a fraction of the width of a human hair.



A patch of microneedles modeled after snake fangs can be used to extract bodily fluid through human skin.



In this modified lateral flow device, a blood sample mixed with reagents wicks up into the exposed porous matrix. Capillary action draws the sample into the 7-centimeter-long device and over the embedded chemical detector. If the substance of interest is present, the detector will change color.

monitor a person's glucose levels. This method eliminates the need for testing blood with painful needle sticks."

Following proper protocols, Mukerjee applied the patch—which he could not feel—to his own arm, drank a soda sweetened with high-fructose corn syrup, and watched his interstitial-fluid glucose levels rise as glucose diffused from the blood into the fluid. UC Davis has licensed this painless technology to a private company, which is now developing a commercial product for use by diabetics.

Integrated Real-Time Detection

In everyday life, people are continuously exposed to various chemicals and compounds that penetrate their bodies via the lungs, digestive track, and skin. These chemicals circulate in the blood system either as primary compounds or as secondary metabolic by-products. Most chemicals present in our bodies are merely part of human dynamic equilibrium, or homeostasis. However, the monitoring of specific circulating chemicals and resultant altered biomolecules may provide a signature that indicates whether a person has been exposed to a material of concern.

Currently, medical staff must either draw blood or collect a urine sample to determine whether a person has been exposed to a dangerous substance. Blood samples can at times take days to analyze. Results from a urine sample can be determined quickly, but some agents can take hours to find their way into the body's urine. For on-the-scene triage by first responders and for optimal follow-up care, a faster and easier-to-use system is essential.

Mukerjee has begun working with chemical engineer Elizabeth Wheeler of the Engineering Directorate to integrate the microneedle fluid-extraction technique with an in situ detection system. Biological systems integration is Wheeler's forte. She has experience with both lateral flow immunoassay methods and DNA sampling.

Lateral flow assay devices draw fluid through a wicking substrate into an immobilized chemical detector. Color change in the chemical detector indicates the presence of a targeted chemical. A home pregnancy test is an example of a simple lateral flow device.

Wheeler was also involved in the development of the BioBriefcase, a prototype system for detecting environmental biological contaminants. The unique DNA preparation methods in the BioBriefcase could be used with the microneedle patch. A bed of silica beads traps the DNA, separating it out from the bits of dirt and other environmental particles that are also in the sample. The DNA is then amplified on the silica surface. This process minimizes the loss of DNA prior to detection.

A Colorful Future

The painless microneedles for fluid sampling combined with colorimetric lateral flow assay technologies will give first responders the tool they need to quickly respond in potential cases of exposure to toxic substances. Another Livermore detection device that first responders are already using is E.L.I.T.E.™ (Easy Livermore Inspection Test for Explosives). (See *S&TR,* October 2006, pp. 16–17.) The E.L.I.T.E. card technology uses a swipe with color-changing detection chemistry. The microneedle detector will incorporate similar technology.

In the future, DNA and RNA detection assays may be incorporated in the microneedle detector. The patch may also be made to detect multiple substances at the same time, a process called multiplexing. Mukerjee adds, "This system may not be the fictional Star Trek tricorder, but our research brings us one tantalizing step closer."

—Katie Walter

Key Words: BioBriefcase, DNA sampling, exposure monitoring, lateral flow assay, microneedle.

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